UNITED STATES ENVIRONMENTAL PROTECTION AGENCY

WASHINGTON, D.C. 20460

OFFICE OF
CHEMICAL SAFETY AND
POLLUTION PREVENTION

MEMORANDUM

DATE: December 12, 2017

SUBJECT: Summary Review of Recent Analysis of Glyphosate Use and Cancer Incidence in the Agricultural Health Study

PC Code: 417300; 103601; 103603; 103604; 103605; 103607; 103608; 103613
DP Barcode: D444727
Decision Number: 487242
Registration Numbers: NA
Petition Number: NA
Regulatory Action: Registration Review
Risk Assessment Type: NA
Case Number: 178
TXR Number: 0057691
CAS Number: 1071-83-6; 38641-94-0; 70393-85-0; 114370-14-8; 40465-76-7; 69254-40-6; 34494-04-7; 70901-12-1
MRID Numbers: NA
40 CFR: 180.364

FROM: Ashlee Aldridge, MPH, Epidemiologist
Toxicology and Epidemiology Branch (TEB)
HED, 7509P

THROUGH: David J. Miller, Branch Chief
TEB/HED (7509P)

TO: Monique M. Perron, Sc.D., Toxicologist
Risk Assessment Branch 1 (RAB1)
HED (7509P)

As part of the Registration Review of glyphosate, summary reviews were completed for epidemiological studies that evaluated the association between glyphosate exposure and risk of numerous cancer outcomes (E. Holman; 7-SEP-2016; D435552; TXR# 0057493). These studies were used as part of an evaluation of the human carcinogenic potential of glyphosate that was presented to the Federal Insecticide, Fungicide, and Rodenticide Act (FIFRA) Scientific Advisory Panel (SAP) in December 2016. Since the SAP meeting, an updated analysis of the Agricultural Health Study (AHS) cohort was published by Andreotti *et al.* (2017). Given this analysis directly informs concerns raised by some panel members regarding the earlier analysis of the AHS cohort (De Roos *et al.*, 2005), particularly with respect to the follow-up period necessary to evaluate risks associated with non-Hodgkin lymphoma (NHL), the Agency has reviewed Andreotti *et al.* (2017) and incorporated the findings into the Revised Glyphosate Issue Paper: Evaluation of Carcinogenic Potential (D444689; TXR# 0057688).

Andreotti, G., Koutros, S., Hofmann, J.N., Sandler, D.P., Lubin, J.H., Lynch, C.F., Lerro, C.C., De Roos, A.J., Parks, C.G., Alavanja, M.C., Silverman, D.T. (2017). Glyphosate use and cancer incidence in the Agricultural Health Study. *JNCI: Journal of the National Cancer Institute*. doi:10.1093/jnci/djx233

In a follow-up study, Andreotti *et al.* (2017) included up to twelve additional years of cancer incidence data through 2012/2013 and four times as many incident cancer cases compared to the previous prospective cohort study conducted by De Roos *et al.* (2005)[1] which was limited to cancer incidence data through 2001. Using data from the Agricultural Health Study (AHS), the study population consisted of male pesticide applicators, and incident cancer cases ascertained through cancer registry files in Iowa (enrollment until 2013) and North Carolina (enrollment until 2012). The following types of cancer were investigated in this study: all cancers, oral cavity, colon, rectum, pancreas, lung, melanoma, prostate, testicular, bladder, kidney, lymphohematopoietic, Hodgkin lymphoma, NHL, NHL B cell, chronic lymphocytic lymphoma, small lymphocytic leukemia, diffuse large B cell lymphoma, marginal-zone lymphoma, follicular lymphoma, multiple myeloma, NHL T cell, acute myeloid leukemia, and chronic myeloid leukemia. Pesticide exposure was assessed via two self-administered questionnaires, one administered during study enrollment (1993 – 1997) and a second follow-up questionnaire administered five years after enrollment (1999 – 2005). Investigators used this questionnaire data to estimate cumulative lifetime days of use and intensity-weighted lifetime days of use[2], and a Poisson regression analysis was used to calculate RRs controlling for age, state of recruitment, cigarette smoking status, alcohol per month, education, family history of cancer, and use of five pesticides most correlated with glyphosate use (alachlor, metolachlor, atrazine, trifluralin, and 2,4-D). For lymphohematopoietic cancers, additional adjustment was performed for occupational exposure to solvents, gasoline, x-ray radiation, and engine exhaust as well as pesticides associated with lymphohematopoietic malignancies in previous AHS analyses (lindane, DDT, diazinon, terbufos, and permethrin). Quartile, tertile, or median categories were created based on intensity-weighted lifetime days (IWLD) of glyphosate exposure relative to each cancer type, and RRs were reported for every category. Additionally, sensitivity analyses were conducted to evaluate the impact of using imputed exposure data for subjects who did not complete the follow-up questionnaire, including analysis using only enrollment exposure data, analysis using data of only participants who completed both the enrollment and follow-up questionnaires, and analysis that truncated the follow-up at 2005. The results of these sensitivity analyses were similar to the main analysis.

Among the total study participants (n = 54,251), 44,932 reported exposure to glyphosate either at enrollment or follow-up, and 5,779 incident cancer cases were identified (four times as many cases as reported in the previous study, De Roos *et al.* 2005). Overall, no evidence of a significant positive association was observed between glyphosate exposure and any type of cancer incidence among pesticide applicators ($0.36 \leq RR \leq 4.25$; all CIs encompassed the null value of 1; n = 5 – 1,451 cases; all p-trends > 0.05). For pancreatic and lung cancer, evidence of a significant positive association was observed in one quartile only relative to intensity-weighted lifetime days (IWLD) of glyphosate exposure (Q1: 1 – 598.9 IWLD: RR: 1.80; 95% CI: 1.05, 3.08, n = 42 cases for pancreatic cancer; Q3: 1650 – 4339.9 IWLD: RR 1.39; 95% CI: 1.07, 1.82, n = 159 cases for lung cancer); however, there was no evidence of a significant positive association in any other quartile for either pancreatic and lung cancer, and a non-statistically

[1] De Roos, A. J., Blair, A., Rusiecki, J. A., Hoppin, J. A., Svec, M., Dosemeci, M., … Alavanja, M. C. (2005). Cancer Incidence among Glyphosate-Exposed Pesticide Applicators in the Agricultural Health Study. *Environmental Health Perspectives*, *113*(1), 49–54. http://doi.org/10.1289/ehp.7340

[2] Cumulative lifetime days of use is the product of years of use and the number of days used per year. Intensity-weighted lifetime days of use is defined as the product of exposure intensity (based on mixing status, application method, equipment repair, and use of personal protective equipment) and lifetime days of use.

significant exposure-response trend was observed for both types of cancer (0.92 ≤ RRs ≤ 1.80; all 95% CIs encompassed the null value of 1; n = 23 – 159 cases; p-trend = 0.14 for pancreatic cancer, p-trend = 0.78 for lung cancer). For acute myeloid leukemia, an elevated but non-statistically significant association was reported in only one quartile (Q4) relative to glyphosate exposure, but there were only a small number of counts in each of the quartiles and the overall p-for-trend was not significant (Q4: ≥ 4340.0 IWLD RR: 2.44; 95% CI: 0.94, 6.32, with n = 18 cases; p-trend = 0.11).

When the data was further stratified by lagged years (5-lag years and 20-lag years) relative to lymphohematopoietic cancers[3] *only*, no evidence of a significant positive association was observed between intensity-weighted lifetime days (IWLD) of glyphosate exposure for any lymphohematopoietic cancer overall. Although evidence of positive association was observed at the 20-year lag median of IWLD of exposure to glyphosate among NHL T cell cancer cases (M1: 1 – 895.90 IWLD RR: 2.97; 95% CI: 1.20, 7.31, n = 9 cases, p-trend = not determined), this is a singular finding and the analysis was limited by the small number of cases observed. In addition, no evidence of a significant positive association was observed at the 5-year lag median for NHL T cell cancer cases (0.96 ≤ RR ≤ 1.86; all 95% CIs encompassed the null value of 1; p-trend = 0.36).

Similarly, for acute myeloid leukemia, evidence of strong positive association was observed in one tertile only (T3) at 20-lag years of IWLD for glyphosate exposure, along with a borderline statistically significant exposure-response trend (T3: ≥1820.0 IWLD RR: 2.04; 95% CI: 1.05, 3.97, n = 15 cases, p-trend = 0.04). However, this analysis was limited by the low number of observed cases. Furthermore, no evidence of a significant positive association was observed in any tertile at 5-lag years for acute myeloid leukemia (1.35 ≤ RR ≤ 2.32; all 95% CIs encompassed the null value of 1; p-trend = 0.07). For the sensitivity analyses, the results indicated no difference between reported exposure data at the two time points (at enrollment only vs. at enrollment and follow-up).

Study strengths included the prospective cohort study design of the AHS and the large number of study participants (n = 54,251). Furthermore, this follow-up study provided a large amount of additional data for glyphosate relative to several types of cancers. In addition, sensitivity analyses were conducted to evaluate the impact of various different analyses and assumptions. The results of these sensitivity analyses were similar to the main analysis. Limitations of the study included: self-reported pesticide usage that potentially led to exposure misclassification; the potential of exposure misclassification due to the imputation of exposure data for 37% of subjects using a data-driven multiple imputation procedure; and multiple comparisons that could have resulted in some chance associations. Also, statistical bias might have resulted from over-parameterized models in the analyses of some diseases where case numbers were small and the number of covariates were large (e.g., as non-Hodgkin lymphoma T cell, acute myeloid leukemia, a variety of lymphohematopoietic cancers, etc.)

[3] The following lymphohematopoietic cancers were reported on in this study: lymphohematopoietic, Hodgkin lymphoma, NHL, NHL B cell, chronic lymphocytic leukemia, small lymphocytic lymphoma, diffuse large B cell lymphoma, marginal-zone lymphoma, follicular lymphoma, multiple myeloma, NHL T cell, acute myeloid leukemia, and chronic myeloid leukemia.